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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/719,277	04/13/2001	Andrea D. Branch	RII-003CPUS	7039

959 7590 09/05/2003

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EXAMINER
WORTMAN, DONNA C

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 09/05/2003

21

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/719,277	BRANCH ET AL.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/3/03; 3/20/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14,24-26,28-31 and 36-51* is/are pending in the application.

4a) Of the above claim(s) *1,14,24-26,28,30,37,45,50 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,31,36,38-44 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,14,24-26,28-31 and 36-51* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 2-13, 15-23, 27 and 32-35 were canceled, claims 28, 29 and 31 were amended, and claims 36-51 were added in Paper No. 15.

Newly submitted claims 37, 41 (in part), 45, 47 (in part), 48 (in part), 49 (in part), 50, and 51 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The claims cited above read on the groups of inventions of record in the previous Office action:

Claims 28, 37, 50, and 51, and claims 31, 38-44, and 46-49, insofar as drawn to a method of detecting antibodies to an HCV +1 reading frame polypeptide, read on the invention of Group VI as set forth in the previous Office action.

Claims 28, 37, 50, and 51, and claims 31, 39-41, and 45-49, insofar as drawn to a method of detecting antibodies to an HCV +2 reading frame polypeptide, read on the invention of Group VII as set forth in the previous Office action.

Claims 29 and 36, and claims 31, 38-44, and 46-49, insofar as drawn to a method of detecting an HCV +1 polypeptide, read on the invention of Group VIII as set forth in the previous Office action.

Claims 29 and 36, and claims 31, 39-41, and 45-49, insofar as drawn to a method of detecting an HCV +2 polypeptide, read on the invention of Group IX as set forth in the previous Office action.

These inventions or groups of inventions are not so linked as to form a single general inventive concept under PCT Rule 13.1 for the reasons previously given.

Applicant's remarks regarding the requirement for restriction and the propriety of examining claims to multiple products and methods under PCT Rule 13 have been noted but not found persuasive. As Applicant has pointed out, a special technical feature defines a contribution which an invention, considered as a whole, makes over the prior art. Applicant has stated that the special technical feature of the pending

claims is that hepatitis C virus produces polypeptides in alternate reading frames, +1 and +2 to the standard open reading frame. Applicant's statement supports a lack of unity since (1) the prior art applied in the previous Office action teaches HCV +1 polypeptide and (2) Applicant has not stated on the record that all HCV +1 and all HCV +2 polypeptides, i.e., all HCV alternate reading frame polypeptides, are clearly unpatentable over each other, i.e., that any art that applies to any HCV +1 polypeptide would apply equally to any HCV +2 polypeptide. Further, once a restriction requirement has been made final, the applicant, in addition to making any reply due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. (See 37 CFR 1.144 and MPEP 818.03(c).)

Since applicant has received an action on the merits for the originally elected invention of Group VIII, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 1, 14, and 24-26; claims 28, 37, 50 and 51; and claims 31, 38-44, and 46-49, insofar as they do not read on the elected invention, are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 29 and 36, and claims 31, 38-44, and 46-49 are under examination insofar as drawn to the elected invention, a method of detecting an HCV +1 polypeptide.

The application is not in complete compliance with the sequence rules. Claims 48 and 49 recite sequences that are not accompanied by SEQ ID NO's as is required by 37 CFR 1.821(d). Correction is needed.

Rejection withdrawn

The rejection of claim 29 under 35 USC 112, first paragraph, for claiming detection of "isolated or recombinant" polypeptide is withdrawn in view of Applicant's amendment to the claim.

Rejections maintained

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29, 36, 31, 38-44, and 46-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, essentially for reasons of record in rejecting claims 29 and 31 in the previous Office action.

Claims 29, 36, 31, 38-44, and 46-49 are under examination insofar as they are drawn to a method of detecting an HCV +1 polypeptide in the body fluid or tissue or in the body fluid of a subject. The specification teaches, in Examples 1 and 2, that certain polypeptides derived from an HCV +1 reading frame detect antibodies that are present in the body fluid of subjects infected with HCV. While the specification teaches that one can use such polypeptides to raise antibodies that may subsequently be used to detect

polypeptides in tissue or body fluids of infected subjects (pages 20-25), the specification does not provide results of such assays that would serve to demonstrate that such polypeptides are actually circulating or present in the body fluids of infected subjects, or that antibodies raised against the disclosed polypeptides actually detect HCV +1 reading frame polypeptides in body fluids or tissues of infected subjects. While methods for raising antibodies and methods for using antibodies to detect polypeptides in conventional immunoassay formats are described, an actual antibody raised against the disclosed polypeptides and an immunoassay that in fact detects the presence of HCV +1 reading frame polypeptide in an infected subject is not described in such a way that one of skill would be able to practice the invention without undue experimentation. In this regard, while the detection of antibodies in patient sera to an HCV +1 viral polypeptide may imply that the polypeptide may be expressed during infection at least in some patients (see, e.g., Varaklioti et al., The Journal of Biological Chemistry 20:17713-17721, 2002, of record), and while patient antisera apparently detect an HCV +1 polypeptide in transfected cell lysates, no structural or functional role for the protein has been described in the viral life cycle, and neither the actual expression of the polypeptide in different HCV isolates during infection *in vivo* nor the presence of the polypeptide in any type of tissue or body fluid sample has been demonstrated either in Applicant's specification, which claims priority to June 1998, or subsequently, using methods that are commensurate with those disclosed by Applicant. See Varaklioti, page 17720, last four paragraphs. Lacking direct evidence that an HCV +1 reading frame polypeptide is present in the body fluid or tissue of an HCV infected subject, the

specification cannot be said to enable one of skill in the art to practice the invention at the time the invention was made, without undue experimentation and with a reasonable expectation for success.

To the extent that Applicant's remarks are deemed to apply to the invention under examination, the remarks will be addressed here.

Applicant has argued that the rejection appears to be based on lack of utility rather than on lack of enablement; that one of skill in the art could readily detect the presence or absence of a polypeptide in the body fluid or tissue of a subject; that exemplary means are taught in the specification at pages 29 and 30 and are known in the art; and that the Examiner has not met the burden to provide reason to doubt "asserted utility."

These arguments have been considered but not found persuasive. The rejection was made based on lack of enablement, i.e., the specification does not teach how to use the invention as claimed, to diagnose HCV infection, without undue experimentation and with a reasonable expectation for success. Clearly the methods to be used to detect polypeptides in body fluid or tissue are generally known in the art. The specification at page 30 generally discloses using antibodies that specifically bind "novel polypeptides" to detect the polypeptides in body fluid or tissue samples. The claims presently recite "detecting the presence or absence of an HCV alternate reading frame polypeptide" which may be of a range of sizes (claims 31, 38, 39, 40, 41, 44, 46, 48, 49) or which may have many possible amino acid sequences (claims 42, 43, 46, 48). However, as pointed out above, the specification does not teach how to diagnose HCV

infection by detecting any of the polypeptides encompassed by the claims, and a document published well after Applicant's priority date states that the role of an alternative reading frame polypeptide in HCV life cycle is not understood. Further, it is appropriate to consider, among other things, the lack of working examples in assessing the amount of experimentation necessary to practice an invention throughout the claimed scope. Applicant has provided argument only, and no factual evidence, that one of skill in the art would know how to practice the claimed invention and to diagnose HCV infection by actually detecting the presence of the polypeptides as recited, without undue experimentation and with a reasonable expectation for success, based only on Applicant's disclosure and what was known in the art at the time the invention was made.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29 and 36, and claims 31, and 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Lo et al. (Virology 199:124-131, 1994), or Lo et al. (Virology 213:455-561, 1995), either in light of Xu et al. (The EMBO Journal 20(14):3840-3848, 2001), all references of record, for reasons of record in rejecting claims 29 and 31 in the previous Office action.

Applicant has argued that since Xu et al. was published after Applicant's priority date, it is not prior art and cannot be used to provide motivation to modify the teachings of the primary references; that Lo B1 does not teach that P16 is expressed in the course of HCV infection and that all of the data in Lo B1 were generated using in vitro translation; that Lo B2 states that P16 and P21 are co-amino terminal, that P16 is a shortened core protein, and that P16 expression was enhanced when E1 envelope was not present; that Lo B2 does not teach that P16 is made during infection.

These arguments have been considered but not found persuasive. That Xu et al. was published after Applicant's filing date was acknowledged in the previous Office action; Xu et al. was cited only as evidence that the prior art HCV protein P16 of Lo et al. is an HCV +1 protein, regardless of whether or not its actual nature was earlier recognized. Xu et al. was not cited to provide motivation to modify the prior art

references. In addition to being expressed in *in vitro* systems, Lo B1 discloses that P16 is also expressed in mammalian cells (page 129, 2nd paragraph under "Discussion"). In response to applicant's argument that Lo B2 states that P16 and P21 are co-amino terminal and thus that the reference fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the alternative reading frame polypeptide as claimed is not co-amino terminal with the HCV core polypeptide) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Neither reference teaches that the P16 protein is only made *in vitro* translation systems; both in fact mention that it is made in mammalian cells. Lo B2 teaches that the production of P16 is enhanced when E1 is not present but does not teach that it is not present when E1 is present. Further, Applicant has presented no factual evidence that the P16 of Lo B1 and Lo B2 is not an HCV +1 reading frame protein, regardless of whether or not it was recognized by Lo B1 or Lo B2 as such.

New rejections

Claims 29 and 36, and claims 31, 38-44, and 46-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims being examined are drawn to the diagnosis of HCV by detection of a genus of

polypeptides that comprise an amino acid sequence encoded by an HCV +1 reading frame. Claims 29, 36, 31, and 41 are drawn to the use of a polypeptide comprising an amino acid sequence encoded by an HCV alternate reading frame. None of the claims are limited to a polypeptide of a particular sequence, since even claims 38, 42, 43, 44, 47, 48, and 49 that recite a sequence recite the open language "comprising." None of the claims are limited to a polypeptide of a particular size, since claims 38, 39, 40, 42, 43, 44, and 46 do not clearly recite any upper limit to the size of the polypeptide. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. With respect to HCV +1 polypeptides and their detection, Applicant has disclosed SEQ ID NO:2, as well as sequences in Table 2 that are very similar to SEQ ID NO:2, and a shorter polypeptide represented by SEQ ID NO:s 3 and 5. It is apparent that Applicant has not described the detection of the genus of HCV+1 polypeptides encompassed by the claims in such a way as to reasonably convey to one skilled in the art that the inventors had possession of a sufficient number of such polypeptides as to represent possession of the invention as claimed. Even if the claims were to be limited to

polypeptides that are at least about 60%-70% identical to SEQ ID NO:2, e.g., as recited in claim 42, it is noted that SEQ ID NO:2 represents 196 amino acids and a polypeptide that is 60% identical could vary by any 70 amino acids. Since it is evident from the sequences presented in Table 2, for example, that no HCV +1 reading frame polypeptides are described that are as little as 60% identical to SEQ ID NO:2, Applicant cannot be said to have provided description that is representative of the entire genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38-40, 42-44, 46 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 is indefinite in reciting "comprising an amino acid sequence encoded by a reading frame corresponding to the reading frame of SEQ ID NO:1" since it is not clear how much amino acid sequence or what amino acid sequence encoded by the reading frame of SEQ ID NO:1 is required at minimum in order to fall within the intended limitations of the claim. Would two amino acids be enough? Would the minimum number of amino acids have to begin with the amino acid encoded by the first codon of SEQ ID NO:1 in order to fall within the intended boundaries of the claim?

Claim 39 is indefinite because it is not clear what "at least about 8 amino acids to at least about 100 amino acids in length" is intended to mean. Is it intended that the minimum length can be either at least about 8 amino acids, i.e., about 8 amino acids or more, or at least about 100 amino acids, i.e., about 100 amino acids or more, with no

maximum length recited, or is it intended to claim a range of sizes of about 8 amino acids or more, up to about 100 amino acids or more in length? If "at least about 100 amino acids" is intended to represent the upper limit of a range, the claim is indefinite since the recitation of "at least" does not specify any upper limit. The metes and bounds of the claim are unclear.

Claim 40 is similarly indefinite in reciting "at least about 14 amino acids" and "at least about 30 amino acids" since one cannot determine what length is intended.

Claim 42 is indefinite in reciting "the polypeptide comprises an amino acid sequence at least about 60-70% identical to the amino acid sequence shown in SEQ ID NO:2 ..." because it is not clear if the intended comparison of the comprised "amino acid sequence" is intended to be made over the entire length of SEQ ID NO:2.

Claim 43 is similarly indefinite in reciting "the polypeptide comprises an amino acid sequence at least about 90% identical to the amino acid sequence shown in SEQ ID NO:2 ..." because it is not clear if the intended comparison of the comprised "amino acid sequence" is intended to be made over the entire length of SEQ ID NO:2.

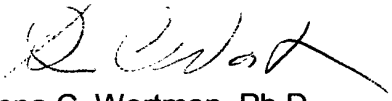
Claim 47 is indefinite because it recites SEQ ID NO:7 and SEQ ID NO:8, which do not appear to be alternate reading frame polypeptides, since they are described in the specification as serving as "controls." It is not clear whether detection of SEQ ID NO:7 and SEQ ID NO:8 is part of the elected invention.

Since this action contains new grounds of rejection, it is made non-final. Any inconvenience is regretted.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 703-308-1032. The examiner can normally be reached on Monday-Thursday, 7:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw
September 4, 2003